(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 056 189 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 20.08.86

(51) Int. Cl.⁴: A 61 K 31/215, A 61 K 31/22, A 61 K 31/23, A 61 K 31/235, C 07 C 69/16, C 07 C 69/28, C 07 C 69/533, C 07 C 69/58, C 07 C 69/587, C 07 C 69/612, C 07 C 69/614

(21) Application number: 81306100.9

(22) Date of filing: 23.12.81

(54) 2,3-Butanediol diester derivatives, process for producing the same, and an antiulcer drug containing the same.

(30) Priority: 26.12.80 JP 186144/80
04.06.81 JP 86034/81
14.07.81 JP 109778/81
02.10.81 JP 157110/81

(43) Date of publication of application:
21.07.82 Bulletin 82/29

(45) Publication of the grant of the patent:
20.08.86 Bulletin 86/34

(84) Designated Contracting States:
CH DE FR GB IT LI

(56) References cited:
GB-A-1 289 535
US-A-4 118 583
US-B- 385 483

HAGERS HANDBUCH DER PHARMAZEUTISCHEN PRAXIS, 4. Ausgabe, 4. Band (1973)

(73) Proprietor: SS PHARMACEUTICAL CO., LTD.
2-12-4 Nihonbashi Hama-cho Chuo-ku
Tokyo (JP)

(72) Inventor: Satoh, Susumu
Yokodo-cho 5-22
Chiba-shi Chiba-ken (JP)
Inventor: Nakashima, Toshiaki
4-4-72 Higashishisui Shisui-machi
Inba-gun Chiba-ken (JP)
Inventor: Mogi, Kinichi
Abiko-588
Abiko-shi Chiba-ken (JP)
Inventor: Murakami, Saburo
Teramachinishiirukudaru Karamaguchi Kita-ku
Kyoto-shi Kyoto-fu (JP)

(74) Representative: Evans, David Charles et al
F.J. CLEVELAND & COMPANY
40-43, Chancery Lane
London, WC2A 1JQ (GB)

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European patent convention).

Courier Press, Leamington Spa, England.

Description

1) Field of the Invention:

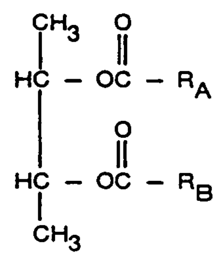
The present invention relates to 2,3-butanediol diester derivatives, process for producing the same, and an antiulcer drug containing the same.

2) Description of the Prior Art:

Heretofore, it has been known that coixenolide, a constituent of coix seed, has an antitumor effect (Japanese Patent Publication No. 36—13349) and some 2,3-butanediol diesters can be used as a durable perfume/flavor agent or modifier (Japanese Patent Laid-open No. 55—154940).

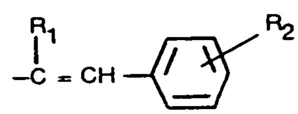
Summary of the Invention

The present inventors have carried out a series of researches on the pharmacological actions of 2,3-butanediol diester derivatives (abbreviated as "butanediol diester" hereunder), and as the result of these researches, they have discovered that the butanediol diester represented by the formula (I)

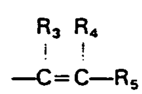


(I)

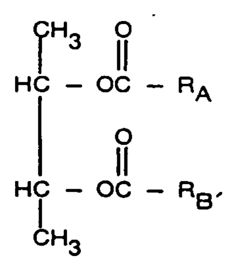
Where R_A is a saturated or unsaturated alkyl group which may have a branched chain, or a group represented by



(where R_1 is a hydrogen atom, cyano group, or lower alkyl group, and R_2 is a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy group, or lower acyloxy group); R_B is a saturated or unsaturated alkyl group which may have a branched chain, phenyl group which may be substituted with lower alkyl group, lower alkoxy group or halogen atom, phenylalkyl group, phenylpropenyl group, phenoxyalkyl group, or a group represented by

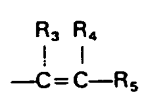


(where R_3 is a hydrogen atom, halogen atom, cyano group, lower alkyl group, or phenyl group, and R_4 is a hydrogen atom, lower alkyl group, or phenyl group, and R_5 is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group, acyloxy group or halogen atom); has an action to depress strongly the growth of peptic ulcer and has a very low toxicity and that among the compounds represented by the formula (I) the compounds are represented by the following formula (II) are novel compounds:



(II)

where R_A is as defined above, R_B' is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group or halogen atom, phenylalkyl group, phenylpropenyl group, phenoxyalkyl group, or a group represented by



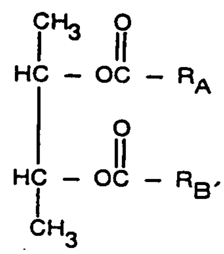
(where R_3 is a hydrogen atom, halogen atom, cyano group, lower alkyl group, or phenyl group, and R_4 is a hydrogen atom, lower alkyl group, or phenyl group, and R_5 is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group, acyloxy group or halogen atom).

Thus according to one aspect of the present invention there is provided the use in the manufacture of an antiulcer drug of a 2, 3-butanediol diester derivative represented by the above formula (I)

In a second aspect of the present invention there is provided an anti-ulcer drug containing as an active ingredient a 2, 3-butanediol diester derivative, other the coixenolide, represented by the above formula (I):

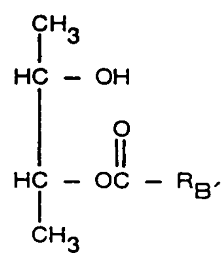
In a third aspect of the present invention there is provided a 2, 3-butanediol diester derivative represented by the above formula (II):

In a fourth aspect of the present invention there is provided a process for preparing a 2, 3-butanediol diester derivative represented by the formula (II):



(II)

where R_A and R_B' are as defined above, said process comprising reacting a 2,3-butanediol monoester derivative represented by the formula (VII):



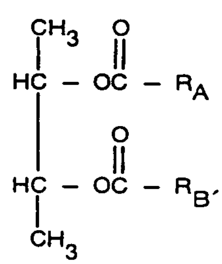
(VII)

where R_B' is as defined above with a carboxylic acid or a reactive derivative thereof represented by the formula (IV):

$$R_ACOOH \qquad (IV)$$

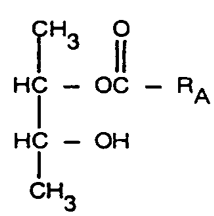
where R_A is as defined above.

In a fifth aspect of the present invention there is provided a process for preparing a 2, 3-butanediol diester derivative represented by the formula (II):



(II)

where R_A and R_B' are as defined above, said process comprising reacting a 2,3-butanediol monoester derivative represented by the formula (V):



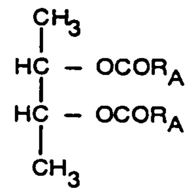
(V)

where R_A is as defined above with a carboxylic acid or active derivative thereof represented by the formula (IV):

$$R_B'COOH \qquad (VI)$$

where R_B' is as defined above.

In a sixth aspect of the invention there is provided a process for preparing a 2, 3-butanediol diester derivative represented by the formula (I'):



(I')

where R_A is as defined above, said process comprising reacting a 2,3-butanediol with a carboxylic acid or reactive derivative thereof represented by the formula (IV):

$$R_ACOOH \qquad (IV)$$

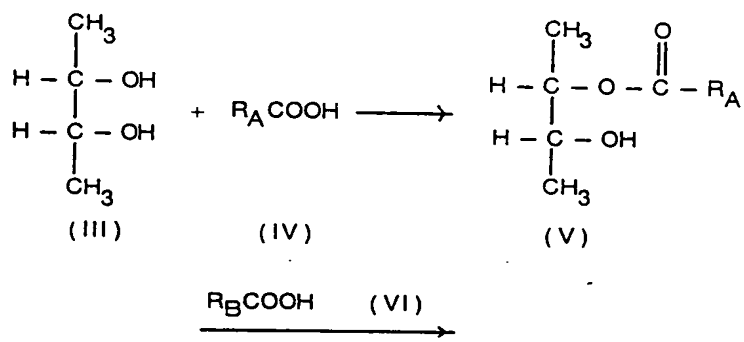
where R_A is as defined above.

Description of the invention and preferred embodiments

The butanediol diester (I) of this invention is a known compound or a novel compound produced by a process based on known reaction or any one of the following processes.

Process for production:—

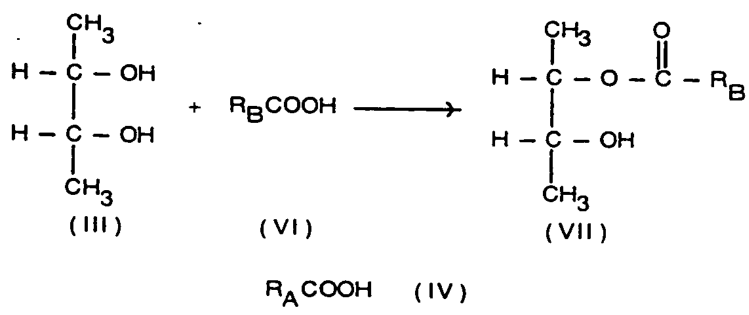
(1) According to this process for the production of a compound of formula (I), 2, 3-butanediol (III) is converted to a 2,3-butanediol monoester derivative (V) by the reaction with a carboxylic acid (IV) or a reactive derivative thereof, and (V) is converted to the object compound (I) by the reaction with a carboxylic acid (VI) or a reactive derivative.



(I)

where R_A and R_B are as defined above.

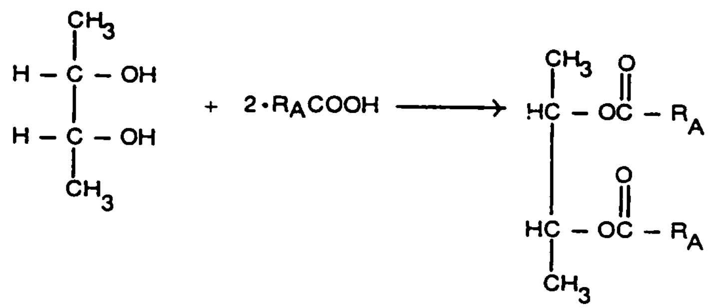
(2) According to a further process for the production of the compound of formula (I), 2, 3-butanediol (III) is converted to a 2, 3-butanediol monoester derivative (VII) by the reaction with a carboxylic acid (VI) or a reactive derivative thereof, and (VII) is converted to the object compound (I) by the reaction with a carboxylic acid (IV).



(I)

where R_A and R_B are as defined above.

(3) According to a further feature of the invention there is provided a process for the production of a compound of the formula (I'), wherein 2, 3-butanediol (III) is converted to a 2, 3-butanediol diester derivative (I') by the reaction with a carboxylic acid (IV) or a reactive derivative thereof, preferably in twofold moles;



(III) (IV) (I')

where R_A is as defined above.

Examples of the reactive derivatives of the carboxylic acids (IV) and (VI) used in these processes include acid halides, acid anhydrides, and mixed acid anhydrides. If these compounds are to be used, the reaction should preferably be carried out in the presence of a deacidifier such as pyridine, tertiary amines, alkali metal carbonates, alkali metal hydroxides, and alkali metal hydrides.

Typical butanediol diesters produced by the above processes are shown in Table 1, in which compounds No. 1 to 21 are known and compounds No. 22 to 81 are novel.

TABLE 1

Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
1	$(CH_2)_6CH_3$	$(CH_2)_6CH_3$	1.436		4.7 – 5.2 (m.2H) 2.3 (t.4H) 1.1 – 1.9 (m.26H) 0.9 (t.6H)
2	$(CH_2)_7CH$	$(CH_2)_7CH_3$	1.439		4.7 – 5.1 (m.2H) 2.2 (t.4H) 1.1 – 1.9 (m.30H) 0.9 (t.6H)
3	$(CH_2)_8CH_3$	$(CH_2)_8CH_3$	1.444		4.7 – 5.2 (m.2H) 2.2 (t.4H) 1.1 – 1.9 (m.34H) 0.9 (t.6H)
4	$(CH_2)_9CH_3$	$(CH_2)_9CH_3$	1.445		4.6 – 5.2 (m.2H) 2.2 (t.4H) 1.1 – 1.9 (m.38H) 0.9 (t.6H)
5	$(CH_2)_{10}CH_3$	$(CH_2)_{10}CH_3$		40 – 42	4.7 – 5.2 (m.2H) 2.3 (t.4H) 1.1 – 1.9 (m.42H) 0.9 (t.6H)
6	$(CH_2)_{12}CH_3$	$(CH_2)_{12}CH_3$		51 – 53	4.7 – 5.2 (m.2H) 2.3 (t.4H) 1.1 – 1.9 (m.50H) 0.9 (t.6H)
7	$(CH_2)_{14}CH_3$	$(CH_2)_{14}CH_3$		55 – 57	4.7 – 5.2 (m.2H) 2.3 (t.4H) 1.1 – 1.8 (m.58H) 0.9 (t.6H)
8	$CH(CH_3)CH_2CH_3$	$CH(CH_3)CH_2CH_3$	1.426		4.6 – 5.2 (m.2H) 2.0 – 2.6 (m.2H) 1.0 – 2.0 (m.16H) 0.9 (t.6H)

TABLE 1 (Continued)

Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm : CCl_4)
9	$\overset{CH_3}{\overset{\vert}{C}}HCH_2CH_2CH_3$	$\overset{CH_3}{\overset{\vert}{C}}HCH_2CH_2CH_3$	1.429		4.7 – 5.2 (m.2H) 2.1 – 2.7 (m.2H) 1.1 (d.6H) 0.7 – 1.8 (m.20H)
10	$CH_2\overset{CH_3}{\overset{\vert}{C}}HCH_2CH_3$	$CH_2\overset{CH_3}{\overset{\vert}{C}}HCH_2CH_3$	1.433		4.7 – 5.2 (m.2H) 2.1 – 2.4 (m.4H) 1.6 – 2.1 (m.2H) 1.1 – 1.5 (m. 4H) 1.2 (d.6H) 0.95 (d.6H) 0.9 (t.6H)
11	$CH_2CH_2\overset{CH_3}{\overset{\vert}{C}}HCH_3$	$CH_2CH_2\overset{CH_3}{\overset{\vert}{C}}H{-}CH_3$	1.432		4.7 – 5.2 (m.2H) 2.4 (t.4H) 1.5 (m.6H) 1.2 (d.6H) 0.9 (d.12H)
12	$CH_2\overset{CH_3}{\overset{\vert}{C}}HCH_2\underset{CH_3}{\underset{\vert}{\overset{CH_3}{\overset{\vert}{C}}}}{-}CH_3$	$CH_2\overset{CH_3}{\overset{\vert}{C}}HCH_2\underset{CH_3}{\underset{\vert}{\overset{CH_3}{\overset{\vert}{C}}}}{-}CH_3$	1.437		4.6 – 5.1 (m.2H) 1.8 – 2.4 (m.6H) 0.8 – 1.5 (m.16H) 0.9 (s.18H)
13	$CH_2CH_2CH = CH_2$	$-CH_2CH_2CH = CH_2$	1.446		5.4 – 6.1 (m.2H) 4.6 – 5.2 (m.3H) 2.3 (m.8H) 1.1 (d.6H)
14	$CH = CH(CH_2)_6CH_3$	$-CH = CH(CH_2)_6CH_3$	1.464		6.5 – 7.1 (m.2H) 5.7 (d.2H) 4.7 – 5.2 (m.2H) 1.9 – 2.5 (m.4H) 1.0 – 1.9 (m.26H) 0.9 (t.6H)
15	$(CH_2)_7CH = CHCH_2-$ $-CH = CH(CH_2)_4CH_3$	$-(CH_2)_7CH = CHCH_2-$ $-CH = CH(CH_2)_4CH_3$	1.471		5.1 – 5.5 (m.8H) 4.6 – 5.1 (m.2H) 2.6 – 3.0 (m.4H) 0.8 – 2.5 (m.56H)

TABLE 1 (Continued)

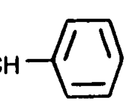
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
16	$(CH_2)_6CH_2-$ $-(CH=CHCH_2)_3CH_3$	$-(CH_2)_6CH_2-$ $-(CH=CHCH_2)_3CH_3$	1.481		5.0 – 5.5 (m.12H) 4.5 – 5.1 (m.2H) 2.5 – 3.0 (m.8H) 0.8 – 2.5 (m.44H)
17	$(CH_2)_9CH_3$	$-(CH_2)_4CH_3$	1.440		4.7 – 5.2 (m.2H) 2.3 (t.4H) 1.1 – 1.9 (m.28H) 0.9 (t.6H)
18	" "	$-(CH_2)_6CH_3$	1.443		4.7 – 5.1 (m.2H) 2.2 (t.4H) 1.1 – 2.0 (m.30H) 0.9 (t.6H)
19	" "	$-(CH_2)_8CH_3$	1.445		4.7 – 5.1 (m.2H) 2.2 (t.4H) 1.1 – 2.0 (m.32H) 0.9(t.6H)
20	" "	$-CH=CHCH_3$ trans	1.450		6.5 – 7.1 (m.1H) 5.75 (m.1H) 4.7 – 5.1 (m.2H) 2.2 (t.2H) 1.9 (dd.3H) 1.1 – 1.8 (m.22H) 0.9 (t.3H)
21	" "	$-(CH_2)_7CH=CH(CH_2)_7$ cis $-CH_3$	1.456		5.0 – 5.5 (m.2H) 4.6 – 5.0 (m.2H) 1.1 – 2.4 (m.52H) 0.9 (t.6H)
22	$-(CH_2)_4CH_3$	$-CH=CH-$ 	1.514		7.6 (d.1H) 7.2 – 7.6 (m.5H) 6.3 (d.1H) 4.7 – 5.3 (m.2H) 2.25 (t.2H) 1.0 – 1.9 (m.12H) 0.9 (t.3H)

TABLE 1 (Continued)

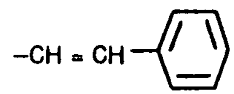
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	MNR (δ ppm.: CCl_4)
23	$-(CH_2)_6CH_3$		1.509		7.6 (d.1H) 7.2 – 7.5 (m.5H) 6.3 (d.1H) 4.7 – 5.3 (m.2H) 2.25 (t.2H) 1.0 – 1.9 (m.16H) 0.9 (t.3H)
24	$-(CH_2)_7CH_3$	,,	1.505		7.6 (d.1H) 7.2 – 7.5 (m.5H) 6.3 (d.1H) 4.7 – 5.3 (m.2H) 2.25 (t.2H) 1.0 – 1.9 (m.18H) 0.9 (t.3H)
25	$-(CH_2)_8CH_3$	,,	1.501		7.7 (d.1H) 7.3 – 7.7 (m.5H) 6.4 (d.1H) 4.8 – 5.7 (m.2H) 2.0 – 2.5 (t.2H) 1.0 – 1.8 (m.20H) 0.9 (t.3H)
26	$-(CH_2)_9CH_3$	,,	1.503		7.6 (d.1H) 7.2 – 7.5 (m.5H) 6.3 (d.1H) 4.7 – 5.2 (m.2H) 2.2 (t.2H) 1.0 – 1.8 (m.22H) 0.9 (t.3H)
27	$-(CH_2)_{10}CH_3$	,,	1.500		7.6 (d.1H) 7.1 – 7.5 (m.5H) 6.3 (d.1H) 4.7 – 5.2 (m.2H) 2.2 (t.2H) 1.0 – 1.8 (m.24H) 0.9 (t.3H)
28	$-(CH_2)_8CH=CH_2$	,,	1.509		7.6 (d.1H) 7.3 (m.5H) 6.35 (d.1H) 5.4 – 6.1 (m.1H) 4.7 – 5.3 (m.4H) 2.2 (t.2H) 1.0 – 2.1 (m.20H)

TABLE 1 (Continued)

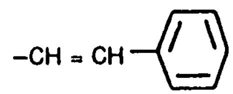
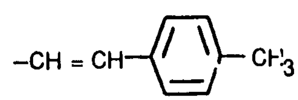
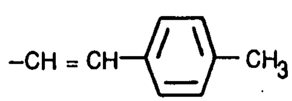
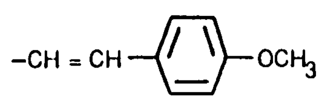
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm : CCl_4)
29	$-(CH_2)_7CH=CH$ $(CH_2)_7CH_3$(cis)		1.503		7.6 (d.1H) 7.1 – 7.5 (m.5H) 6.8 (d.1H) 5.1 – 5.4 (m.2H) 4.8 – 5.1 (m.2H) 1.0 – 2.4 (m.34H) 0.9 (t.3H)
30	$-(CH_2)_7CH=CH$ $(CH_2)_7CH_3$(trans)	,,	1.505		7.65 (d.1H) 7.2 – 7.5 (m.5H) 6.35 (d.1H) 5.2 – 5.5 (m.2H) 4.9 – 5.2 (m.2H) 1.1 – 2.5 (m.34H) 0.9 (t.3H)
31	$-(CH_2)_4CH_3$		1.504		7.55 (d.1H) 7.3 (d.1H) 7.05 (d.1H) 6.3 (d.1H) 4.7 – 5.2 (m.1H) 2.3 (s.3H) 2.0 – 2.4 (t.2H) 1.0 – 2.0 (m.12H) 0.9 (t.3H)
32	$-(CH_2)_9CH_3$	,,	1.499		7.5 (d.1H) 7.35 (d.2H) 7.05 (d.2H) 6.25 (d.1H) 4.7 – 5.3 (m.2H) 2.35 (s.3H) 2.2 (t.2H) 1.1 – 1.9 (m.22H) 0.9 (t.3H)
33		,,		72 – 74	7.5 (d.2H) 7.35 (d.4H) 7.15 (d.4H) 6.35 (d.2H) 4.7 – 5.1 (m.2H) 2.3 (s.6H) 1.4 (d.6H)
34	$-(CH_2)_4CH_3$		1.528		7.5 (d.1H) 7.4 (d.2H) 6.8 (d.2H) 6.15 (d.1H) 4.7 – 5.3 (m.2H) 3.8 (s.3H) 2.2 (t.2H) 1.0 – 1.9 (m.12H) 0.9 (t.3H)

TABLE 1 (Continued)

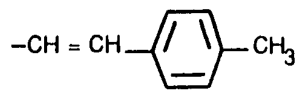
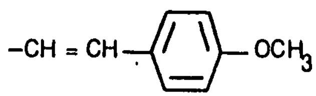
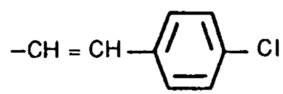
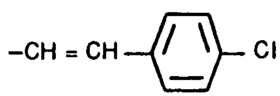
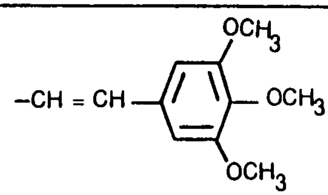
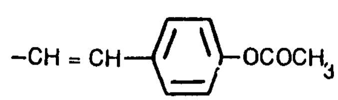
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
35	$-(CH_2)_9CH_3$		1.519		7.5 (d.1H) 7.4 (d.2H) 6.8 (d.2H) 6.15 (d.1H) 4.7 – 5.2 (m.2H) 3.8 (s.3H) 2.2 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
36		"		115 – 117	7.6 (d.2H) 7.4 (d.2H) 7.3 (d.2H) 6.3 (d.2H) 4.9 – 5.4 (m.2H) 3.8 (s.6H) 1.4 (d.6H)
37	$-(CH_2)_4CH_3$		1.524		7.6 (d.1H) 7.4 (d.d.4H) 6.35 (d.1H) 4.8 – 5.4 (m.2H) 2.3 (t.3H) 1.1 – 1.9 (m.12H) 0.9 (t.3H)
38	$-(CH_2)_9CH_3$	"	1.514		7.6 (d.1H) 7.4 (d.d.4H) 6.35 (d.1H) 4.8 – 5.4 (m.2H) 2.3 (t.3H) 1.1 – 1.9 (m.22H) 0.9 (t.3H)
39		"		133 – 136	7.6 (d.2H) 7.3 (m.8H) 6.3 (d.2H) 4.9 – 5.4 (m.2H) 1.3 (d.6H)
40	$-(CH_2)_9CH_3$		1.520		7.45 (d.1H) 6.65 (s.2H) 6.2 (d.1H) 4.8 – 5.3 (m.2H) 3.78 (d.9H) 2.2 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
41	$-(CH_2)_9CH_3$		1.507		7.55 (d.1H) 7.5 (d.2H) 7.05 (d.2H) 6.3 (d.1H) 4.7 – 5.2 (m.2H) 2.25 (s.3H) 2.2 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)

TABLE 1 (Continued)

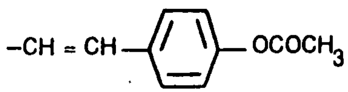
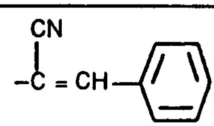
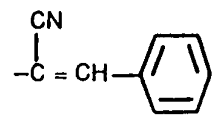
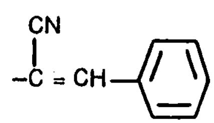
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
42				112 – 116	7.6 (d.2H) 7.45 (d.4H) 7.05 (d.4H) 6.3 (d.2H) 5.0 – 5.4 (m.2H) 2.3 (s.6H) 1.35 (d.6H)
43				177 – 180	8.25 (s.2H) 7.8 – 8.1 (m.4H) 7.3 – 7.7 (m.6H) 5.1 – 5.5 (m.2H) 1.4 (d.6H)
44	$-(CH_2)_4CH_3$	"	1.523		8.15 (s.1H) 7.7 – 8.1 (m.2H) 7.2 – 7.7 (m.3H) 4.7 – 5.4 (m.2H) 2.25 (t.2H) 1.0 – 1.9 (m.12H) 0.9 (t.3H)
45	$-(CH_2)_6CH_3$	"	1.509		8.15 (s.1H) 7.7 – 8.1 (m.2H) 7.3 – 7.7 (m.3H) 4.8 – 5.3 (m.2H) 2.25 (t.2H) 1.0 – 2.0 (m.16H) 0.9 (t.3H)
46	$-(CH_2)_7CH_3$	"	1.516		8.2 (s.1H) 7.8 – 8.1 (m.2H) 7.3 – 7.7 (m.3H) 4.7 – 5.3 (m.2H) 2.3 (t.2H) 1.0 – 1.8 (m.18H) 0.9 (t.3H)
47	$-(CH_2)_8CH_3$		1.514		8.15 (s.1H) 7.7 – 8.1 (m.2H) 7.2 – 7.7 (m.3H) 4.7 – 5.4 (m.2H) 2.25 (t.2H) 1.0 – 1.9 (m.20H) 0.9 (t.3H)

TABLE 1 (Continued)

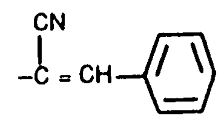
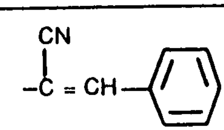
Compound No.	RA	RB	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
48	$-(CH_2)_9CH_3$		1.514		8.13 (s.1H) 7.7 – 8.1 (m.2H) 7.3 – 7.7 (m.3H) 4.8 – 5.3 (m.2H) 2.0 – 2.5 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
49	$-(CH_2)_{10}CH_3$	"	1.512		8.1 (s.1H) 7.8 – 8.1 (m.2H) 7.3 – 7.6 (m.3H) 4.8 – 5.4 (m.2H) 2.3 (t.2H) 1.1 – 1.7 (m.24H) 0.9 (t.3H)
50	$-CH=CHCH_3$	"		78 – 81	8.1 (s.1H) 7.7 – 8.1 (m.2H) 7.3 – 7.6 (m.3H) 6.6 – 7.1 (m.1H) 5.6 – 6.0 (m.1H) 4.7 – 5.3 (m.2H) 1.85 (d.d.3H) 1.30 (d.3H) 1.25 (d.3H)
51	$-C(CH_3)=CHCH_3$	"	1.550		8.1 (s.1H) 7.7 – 8.1 (m.2H) 7.3 – 7.6 (m.3H) 6.5 – 7.0 (m.1H) 4.8 – 5.4 (m.2H) 1.8 (s.3H) 1.75 (d.3H) 1.35 (d.3H) 1.3 (d.3H)
52	$-(CH_2)_7CH=CH(CH_2)_7CH_3$ (cis)	"	1.509		8.1 (d.1H) 7.7 – 8.0 (m.2H) 7.2 – 7.6 (m.3H) 4.7 – 5.4 (m.4H) 1.0 – 2.4 (m.34H) 0.9 (t.3H)
53	$-(CH_2)_7CH=CH(CH_2)_7-CH_3$ (Trans)				8.1 (s.1H) 7.7 – 8.0 (m.2H) 7.2 – 7.6 (m.3H) 4.7 – 5.4 (m.4H) 1.0 – 2.4 (m.34H) 0.9 (t.3H)

TABLE 1 (Continued)

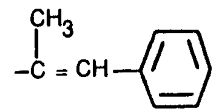
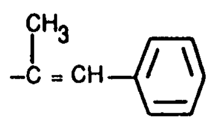
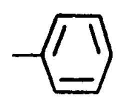
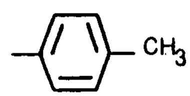
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm : CCl_4)
54	$-(CH_2)_4CH_3$		1.506		7.6 (m.1H) 7.3 (b.s.5H) 4.8 – 5.3 (m.2H) 2.25 (t.2H) 2.1 (d.3H) 1.0 – 2.0 (m.12H) 0.9 (t.3H)
55	$-(CH_2)_9CH_3$	"	1.501		7.6 (m.1H) 7.34 (b.s.5H) 4.8 – 5.3 (m.2H) 2.25 (t.2H) 2.1 (d.3H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)
56	$-(CH_2)_{10}CH_3$	"	1.500		7.6 (m.1H) 7.3 (b.s.5H) 4.8 – 5.3 (m.2H) 2.25 (t.2H) 2.1 (d.3H) 1.0 – 2.0 (m.2H) 0.9 (t.3H)
57		"	1.559		7.6 (m.1H) 7.3 (b.s.5H) 4.9 – 5.4 (m.2H) 2.1 (m.6H) 1.4 (d.6H)
58	$-(CH_2)_4CH_3$		1.480		7.8 – 8.2 (m.2H) 7.2 – 7.7 (m.3H) 4.7 – 5.3 (m.2H) 2.2 (t.2H) 1.0 – 1.9 (m.12H) 0.9 (t.3H)
59	"		1.481		7.8 (d.2H) 7.1 (d.2H) 4.7 – 5.3 (m.2H) 2.3 (s.3H) 2.0 – 2.4 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)

TABLE 1 (Continued)

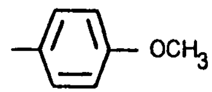
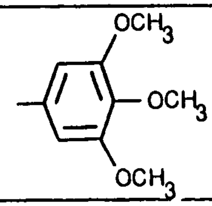
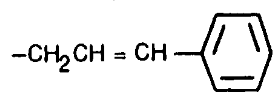
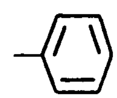
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
60	$-(CH_2)_4CH_3$		1.492		7.9 (d.2H) 6.9 (d.2H) 4.8 – 5.4 (m.2H) 3.8 (s.3H) 2.0 – 2.4 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)
61	"		1.492		7.7 (d.2H) 7.2 (d.2H) 4.7 – 5.3 (m.2H) 2.0 – 2.4 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)
62	"		1.493		7.2 (s.2H) 4.8 – 5.4 (m.2H) 3.8 (d.9H) 2.2 (t.2H) 1.0 – 2.0 (m.12H) 0.9 (t.3H)
63	"		1.498		7.0 – 7.5 (m.5H) 6.0 – 6.6 (m.2H) 4.6 – 5.2 (m.2H) 3.2 (d.2H) 2.0 – 2.4 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)
64	$-(CH_2)_9CH_3$		1.477		7.8 – 8.2 (m.2H) 7.2 – 7.7 (m.3H) 4.7 – 5.4 (m.2H) 2.2 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
65	"		1.481		7.75 (d.2H) 7.05 (d.2H) 4.7 – 5.3 (m.2H) 2.4 (s.3H) 2.2 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)

TABLE 1 (Continued)

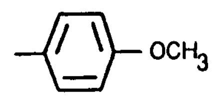
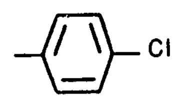
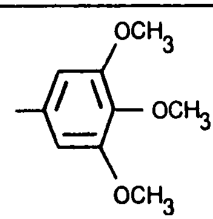
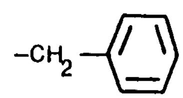
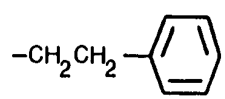
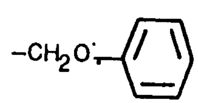
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
66	$-(CH_2)_9CH_3$		1.488		7.9 (d.2H) 6.8 (d.2H) 4.8 – 5.4 (m.2H) 3.8 (s.3H) 2.2 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)
67	"		1.488		7.85 (d.2H) 7.3 (d.2H) 4.7 – 5.3 (m.2H) 2.2 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)
68	"		1.491		7.15 (s.2H) 4.8 – 5.4 (m.2H) 3.8 (d.9H) 2.2 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)
69	"		1.475		7.2 (m.5H) 4.6 – 5.1 (m.2H) 3.5 (s.2H) 2.1 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
70	$-(CH_2)_9CH_3$		1.475		7.15 (s.5H) 4.7 – 5.2 (m.2H) 2.8 (t.2H) 2.7 (t.2H) 2.2 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)
71	"		1.478		6.7 – 7.4 (m.5H) 4.7 – 5.2 (m.2H) 4.5 (s.2H) 2.2 (t.2H) 1.0 – 1.9 (m.22H) 0.9 (t.3H)

TABLE 1 (Continued)

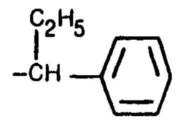
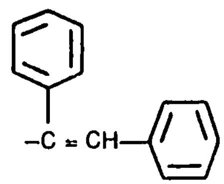
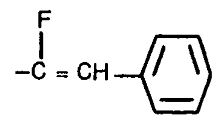
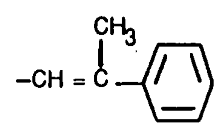
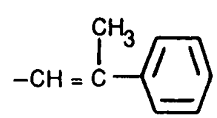
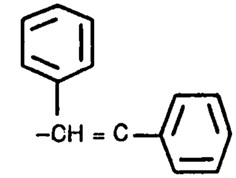
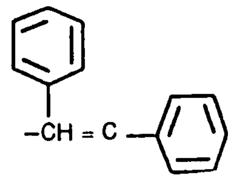
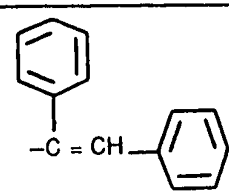
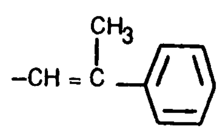
Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
72	$-(CH_2)_9CH_3$		1.474		7.2 (s.5H) 4.6 – 5.1 (m.2H) 3.3 (t.1H) 0.6 – 2.3 (m.28H)
73	$-(CH_2)_4CH_3$		1.536		7.65 (s.1H) 6.8 – 7.4 (m.10H) 4.7 – 5.3 (m.2H) 2.0 – 2.5 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)
74	$-(CH_2)_9CH_3$	,,	1.525		7.6 (s.1H) 6.7 – 7.3 (m.10H) 4.7 – 5.1 (m.2H) 2.0 – 2.4 (t.2H) 1.1 – 2.0 (m.22H) 0.9 (t.3H)
75	$-(CH_2)_4CH_3$		1.496		7.1 – 7.8 (m.5H) 6.8 (d.1H) 4.7 – 5.3 (m.2H) 2.3 (t.2H) 1.1 – 2.0 (m.12H) 0.9 (t.3H)
76	,,		1.506		7.30 (m.5H) 6.15 (m.1H) 4.8 – 5.3 (m.2H) 2.56 (m.3H) 2.30 (t.2H) 1.1 – 1.9 (m.12H) 0.86 (t.3H)
77	$-(CH_2)_9CH_3$		1.495		7.32 (m.5H) 6.10 (m.1H) 4.8 – 5.3 (m.2H) 2.58 (m.3H) 2.30 (t.2H) 1.0 – 1.9 (m.22H) 0.89 (t.3H)

TABLE 1 (Continued)

Compound No.	R_A	R_B	n_D^{20}	Melting point °C	NMR (δ ppm: CCl_4)
78	$-(CH_2)_4CH_3$		1.539		7.21 (s.10H) 6.30 (s.1H) 4.5 – 5.2 (m.2H) 2.28 (t.2H) 1.2 – 1.9 (m.6H) 1.08 (d.6H) 0.89 (t.3H)
79	$-(CH_2)_9CH_3$		1.520		7.22 (s.10H) 6.30 (s.1H) 4.6 – 5.2 (m.2H) 2.30 (t.2H) 1.2 – 1.9 (m.16H) 1.10 (d.6H) 0.9 (t.3H)
80	$-(CH_2)_6CH_3$		1.525		7.7 (s.1H) 6.8 – 7.5 (m.10H) 4.7 – 5.3 (m.2H) 2.25 (t.2H) 1.0 – 2.0 (m.18H) 0.9 (t.3H)
81	"		1.498		7.0 – 7.5 (m.5H) 6.0 (m.1H) 4.6 – 5.2 (m.2H) 2.5 (m.3H) 2.2 (t.2H) 1.0 – 2.0 (m.18H) 0.9 (t.3H)

The butanediol diester (I) is described below with respect to its antiulcer action and acute toxicity.

(i) Antiulcer action

Wister male rats each weighing about 200 g were given, after fasting for 24 hours, orally 25 mg/kg of indomethacin suspended in 1% aq. solution of sodium carboxymethylcellulose. Five hours later, 1 ml of physiological saline containing 2% brilliant blue was injected intravenously in their tails, and 10 minutes later, they were slaughtered and their stomachs were removed. After fixation by injecting 12 ml of 1% formalin aq. solution, the stomachs were extended on a flat plate and the injured parts on the stomach was measured with slide calipers. The sum of the lengths in mm was regarded as the ulcer index.

The test compound was emulsified or suspended in physiological saline containing one drop of polysolvate 80, and this was given orally or subcutaneously in the back one hour before administration of indomethacin.

The ulcer inhibition ratio was obtained from the following formula.

$$\text{Inhibition ratio (\%)} = A/B \times 100$$

A: (ulcer index of control group) — (ulcer index of test group given the test compound)
B: (ulcer index of control group)
The results are shown in Table 2, in which the compound numbers correspond to those in Table 1.

TABLE 2

Compd. No.	No. of rats	Dosage (mg/kg)	Route	Inhibition ratio (%)
1	5	200	Subcutaneously	92
2	"	"	"	90
3	"	"	"	50
4	"	"	"	74
6	"	"	"	57
7	"	"	"	30
15	"	"	"	47
16	"	"	"	86
17	"	"	"	37
22	"	"	"	91
24	"	"	"	90
25	"	"	"	95
28	"	"	"	62
31	"	"	"	91
34	"	"	"	75
35	"	"	"	77
37	"	"	"	85
40	"	"	"	99
45	"	"	"	84
46	"	"	"	56

TABLE 2 (continued)

Compd. No.	No. of rats	Dosage (mg/kg)	Route	Inhibition ratio (%)
48	4	„	Orally	84
„	5	300	Subcutaneously	96
54	„	200	„	87
57	„	„	„	80
60	„	„	„	41.4
62	„	„	„	50.0
64	„	„	„	41.3
68	„	„	„	89.3
70	„	„	„	45.9
71	„	„	„	59.2

As Table 2 indicates, all of the test compounds are apparently effective in antiulcer action.

(ii) Acute toxicity

ddy male mice, arranged in groups each consisting of five mice, were given intraperitoneally 1000 mg/kg of the test compounds Nos. 1—4, 8—10, 14—18, 21, 22, 24, 25, 28, 31, 34, 35, 37, 45, 46, 48, 54, 57, 60, 62, 64, 68, 70, and 71 (as shown in Table 1) dissolved in cotton seed oil. After observation for seven days, all the mice lived without any anomaly. The test compounds were found to have an LD_{50}a higher than 1000 mg/kg and a very low toxicity.

The antiulcer drug of this invention can be administered either orally or non-orally in the form of powder, tablets, capsules, granules, solutions, injections (subcutaneous, intramuscular, intravenous), transfusion, and suppositories.

The above-mentioned preparations can be manufactured by the known methods. Powder, tablets, capsules, and granules can be prepared combining butanediol diester with a diluting agent such as starch, lactose, and mannitol; a binder such as sodium carboxymethylcellulose and hydroxypropylcellulose; a disintegrator such as crystalline cellulose and calcium carboxymethylcellulose; a lubricant such as talc and magnesium stearate; and a fluidity improving agent such as light silicic anhydride. Solutions and injections can be prepared by dissolving butanediol diester in olive oil or peanut oil, or by dissolving or suspending butanediol diester in water or physiological saline using an anionic surface active agent such as polysolvate 60 and polysolvate 80. Suppositories can be prepared by dispersing butanediol diester in cacao butter or synthetic fats in the conventional manner.

The antiulcer drug thus prepared is administered at the dosage of 0.1 to 1000 mg/kg (orally) and 0.05 to 500 mg/kg (non-orally) once to several times a day for adults.

The invention is illustrated by the following examples.

Example 1

(Synthesis of Compound No. 22)

1) Dissolve 9 g (0.1 mole) of 2,3-butanediol in 50 ml of ether.
2) Add 10 ml of pyridine.
3) With stirring and ice cooling, add dropwise 30 ml of ether solution containing 16.65 g (0.1 mole) of cinnamoyl chloride.
4) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 4 hours.
5) Add water and separate the ether layer.
6) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
7) Dry the solution with anhydrous sodium sulfate.
8) Remove ether by distillation under reduced pressure.

9) Purify the residue by column chromatography (SiO_2) to give 9.4 g of colorless liquid monoester (yield 42.7%).

10) Dissolve 9.4 g (0.043 mole) of this monoester in 120 ml of ether.

11) Add 6.8 ml of pyridine.

12) With stirring and ice cooling, add dropwise 120 ml of ether solution containing 5.75 g (0.043 mole) of caproyl chloride.

13) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 4 hours.

14) Add water and separate the ether layer.

15) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.

16) Dry the solution with anhydrous sodium sulfate.

17) Remove ether by distillation under reduced pressure.

18) Purify the residue by column chromatography (SiO_2) to give 9.3 g of colorless liquid which is identified as compound No. 22 in Table 1 (yield 71%).

$$n_D^{20}\ 1.514,\ \text{IR}\ \nu_{max}^{neat}\ \text{cm}^{-1}\ 1720\ (\text{C=O})$$

Example 2

(Synthesis of compound No. 35)

1) With stirring and ice cooling, add dropwise 40 ml of ether solution containing 9 g (0.1 mole) of 2,3-butanediol to 40 ml of ether in which 4 g (0.1 mole) of sodium hydride, is suspended.

2) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 30 minutes.

3) With ice cooling again, add dropwise 40 ml of ether solution containing 20.45 g (0.1 mole) of undecanoyl chloride.

4) Stir at room temperature for 3 hours.

5) Add water and separate the ether layer.

6) Carry out the same steps as in Example 1 to give 10.5 g of colorless liquid monoester (yield 40.7%).

7) Dissolve 10.32 g (0.04 mole) of this monoester in 80 ml of tetrahydrofuran.

8) Add 6.4 ml of pyridine.

9) With stirring and ice cooling, add dropwise 80 ml of tetrahydrofuran solution containing 7.86 g (0.04 mole) of p-methoxycinnamoyl chloride.

10) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 4 hours.

11) Remove the solvent by distillation under reduced pressure.

12) Dissolve the residue in chloroform.

13) Wash the chloroform solution with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.

14) Dry the solution with anhydrous sodium sulfate.

15) Remove chloroform by distillation under reduced pressure.

16) Purify the residue by column chromatography (SiO_2) to give 6 g of colorless liquid which is identified as compound No. 35 in Table 1 (yield 35.8%).

$$n_D^{20}\ 1.519,\ \text{IR}\ \nu_{max}^{neat}\ \text{cm}^{-1}\ 1720\ (\text{C=O})$$

Example 3

(Synthesis of compound No. 43)

1) Dissolve 4.5 g (0.05 mole) of 2,3-butanediol in 60 ml of tetrahydrofuran.

2) Add 10 ml of pyridine.

3) With stirring and ice cooling, add dropwise 60 ml of tetrahydrofuran solution containing 19.15 g (0.1 mole) of α-cyanocinnamoyl chloride.

4) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 4 hours.

5) Remove the solvent by distillation under reduced pressure.

6) Dissolve the residue in chloroform.

7) Wash the chloroform solution with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.

8) Dry the solution with anhydrous sodium sulfate.

9) Remove chloroform by distillation under reduced pressure.

10) Recrystallize the residue from benzene to give 12.4 g of light yellow needle crystal, which is identified as compound No. 43 in Table 1 (yield 62.%).

Melting point: 177 to 180°C

$$\text{IR}\ \nu_{max}^{KBr}\ \text{cm}^{-1}\ 1720\ (\text{C=O})$$

Example 4

(Synthesis of compound 60)

1) With stirring and ice cooling, add 40 ml of ether solution containing 6.3 g (0.07 mole) of 2,3-butanediol to 40 ml of ether in which 3.0 g (0.075 mole) of sodium hydride is suspended.
2) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 30 minutes.
3) With ice cooling again, add dropwise 40 ml of ether solution containing 11.9 g (0.07 mole) of p-anisoyl chloride.
4) Stir at room temperature for 3 hours.
5) Add water and separate the ether layer.
6) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
7) Dry the ether with anhydrous sodium sulfate.
8) Remove ether by distillation under reduced pressure.
9) Purify the residue by column chromatography (SiO_2) to give 6.8 g of colorless liquid monoester (yield 43.4%).
10) Dissolve 2.02 g (0.009 mole) of this monoester in 20 ml of ether.
11) Add 2 ml of pyridine.
12) With stirring and ice cooling, add dropwise 20 ml of ether solution containing 1.22 g (0.009 mole) of n-caproyl chloride.
13) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 3 hours.
14) Add water and separate the ether layer.
15) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
16) Dry the solution with anhydrous sodium sulfate.
17) Remove ether by distillation under reduced pressure.
18) Purify the residue by column chromatography (SiO_2) to give 2.7 g of colorless liquid which is identified as compound No. 60 in Table 1 (yield 93.2%).

$$n_D^{20}\ 1.492,\ \text{IR}\ \nu_{max}^{neat}\ cm^{-1}\ 1720\ (C{=}O)$$

Example 5

(Synthesis of compound 68)

1) With stirring and ice cooling, add 20 ml of ether solution containing 2.7 g (0.03 mole) of 2,3-butanediol to 40 ml of tetrahydrofuran in which 1.2 g (0.03 mole) of sodium hydride is suspended.
2) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 30 minutes.
3) With ice cooling again, add dropwise 40 ml of tetrahydrofuran solution containing 6.92 g (0.03 mole) of 3,4,5-trimethoxybenzoyl chloride.
4) Stir at room temperature for 5 hours.
5) Remove the solvent by distillation under reduced pressure.
6) Dissolve the residue in chloroform.
7) Wash the chloroform layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
8) Dry the chloroform layer with anhydrous sodium sulfate.
9) Remove chloroform by distillation under reduced pressure.
10) Purify the residue by column chromatography (SiO_2) to give 3.66 g of colorless liquid monoester (yield 43%).
11) Dissolve 2.84 g (0.01 mole) of this monoester in 20 ml of ether.
12) Add 2 ml of pyridine.
13) With ice cooling, add dropwise 20 ml of ether solution containing 2.05 g (0.01 mole) of undecanoyl chloride.
14) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 3 hours.
15) Add water and separate the ether layer.
16) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
17) Dry the ether layer with anhydrous sodium sulfate.
18) Remove ether by distillation under reduced pressure.
19) Purify the residue by column chromatography (SiO_2) to give 2.04 g of colorless liquid which is identified as compound No. 68 in Table 1 (yield 50%).

$$n_D^{20}\ 1.491,\ \text{IR}\ \nu_{max}^{neat}\ cm^{-1}\ 1720\ (C{=}O)$$

Example 6

(Synthesis of Compound No. 70)

1) Dissolve 9 g (0.1 mole) of 2,3-butanediol in 50 ml of ether.
2) Add 10 ml of pyridine.
3) With stirring and ice cooling, add dropwise 75 ml of ether solution containing 20.5 g (0.1 mole) of undecanoyl chloride.
4) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 4 hours.
5) Add water and separate the ether layer.
6) Carry out the treatment as in Example 4 to give 13.2 g of colorless liquid monoester (yield 51%).
7) Dissolve 12.9 g (0.05 mole) of this monoester in 100 ml of ether.
8) Add 10 ml of pyridine.
9) With stirring and ice cooling, add dropwise 100 ml of ether solution containing 8.43 g (0.05 mole) of phenylpropionyl chloride.
10) Continue stirring at the cooled temperature for 30 minutes and further continue stirring at room temperature for 3 hours.
11) Add water and separate the ether layer.
12) Wash the ether layer with water, 10% hydrochloric acid, water, saturated sodium hydrogen carbonate solution, and water in the order listed.
13) Dry the solution with anhydrous sodium sulfate.
14) Remove ether by distillation under reduced pressure.
15) Purify the residue by column chromatography (SiO_2) to give 16.2 g of colorless liquid which is identified as compound No. 70 in Table 1 (yield 85.3%).

$$n_D^{20}\ 1.475,\ \text{IR}\ \nu_{max}^{neat}\ cm^{-1}\ 1720\ (C{=}O)$$

Example 7

(Preparation of tablet)

A tablet of the following composition was prepared according to the conventional manner.

Butanediol diester (Compound No. 1 in Table 1)	100 mg
Light silicic anhydride	100 mg
Crystalline cellulose	50 mg
Hydroxypropyl cellulose	10 mg
Calcium carboxymethylcellulose	25 mg
Talc	4 mg
Magnesium stearate	2 mg
Lactose	An amount sufficient to bring the final weight to 350 mg

Example 8

(Preparation of granules)

Granules of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 1 in Table 1)	100 mg
Light silicic anhydride	100 mg
Mannitol	650 mg
Starch	135 mg
Polyvinyl pyrrolidone	15 mg
Total	1000 mg

Example 9

(Preparation of injection)

An oil injection of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 2 in Table 1)	100 mg
Peanut oil	1900 mg
Total	2000 mg

Example 10

(Preparation of suppository)

A suppository of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 2 in Table 1)	100 mg
Cacao butter	1000 mg
Total	1100 mg

Example 11

(Preparation of tablet)

A tablet of the following composition was prepared according to the conventional manner.

Butanediol diester (Compound No. 31 in Table 1)	100 mg
Light silicic anhydride	100 mg
Crystalline cellulose	50 mg
Hydroxypropyl cellulose	10 mg
Calcium carboxymethylcellulose	25 mg
Talc	4 mg
Magnesium stearate	2 mg
Lactose	An amount sufficient to bring the final weight to 350 mg

Example 12

(Preparation of granules)

Granules of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 25 in Table 1)	100 mg
Light silicic anhydride	100 mg
Mannitol	650 mg
Starch	135 mg
Polyvinyl pyrrolidone	15 mg
Total	1000 mg

Example 13

(Preparation of injection)

An oil injection of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 31 in Table 1)	100 mg
Peanut oil	1900 mg
Total	2000 mg

Example 14

(Preparation of suppository)

A suppository of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 40 in Table 1)	100 mg
Cacao butter	1000 mg
Total	1100 mg

Example 15

(Preparation of tablet)

A tablet of the following composition was prepared according to the conventional manner.

Butanediol diester (Compound No. 68 in Table 1)	100 mg
Light silicic anhydride	100 mg
Crystalline cellulose	50 mg
Hydroxypropyl cellulose	10 mg
Calcium carboxymethylcellulose	25 mg
Talc	4 mg
Magnesium stearate	2 mg
Lactose	An amount sufficient to bring the final weight to 350 mg

Example 16

(Preparation of granules)

Granules of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 62) in Table 1)	100 mg
Light silicic anhydride	100 mg
Mannitol	650 mg
Starch	135 mg
Polyvinyl pyrrolidone	15 mg
Total	1000 mg

Example 17

(Preparation of injection)

An oil injection of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 71 in Table 1)	100 mg
Peanut oil	1900 mg
Total	2000 mg

Example 18

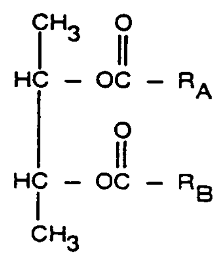
(Preparation of suppository)

A suppository of the following composition were prepared according to the conventional manner.

Butanediol diester (Compound No. 68 in Table 1)	100 mg
Cacao butter	1000 mg
Total	1100 mg

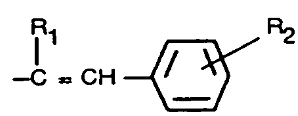
Claims

1. The use in the manufacture of an antiulcer drug of a 2,3-butanediol diester derivative represented by the formula (I):

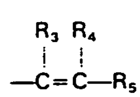


(I)

where R_A is a saturated or unsaturated alkyl group which may have a branched chain, or a group represented by



(where R_1 is a hydrogen atom, cyano group, or lower alkyl group, and R_2 is a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy group, or lower acyloxy group); R_B is a saturated or unsaturated alkyl group which may have a branched chain, phenyl group which may be substituted with lower alkyl group, lower alkoxy group or halogen atom, phenylalkyl group, phenylpropenyl group, phenoxyalkyl group, or a group represented by

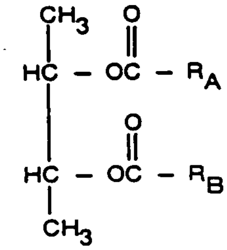


(where R_3 is a hydrogen atom, halogen atom, cyano group, lower alkyl group, or phenyl group, and R_4 is a hydrogen atom, lower alkyl group, or phenyl group, and R_5 is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group, acyloxy group or halogen atom).

2. A use as claimed in Claim 1 wherein the drug is processed into a form for oral administration.

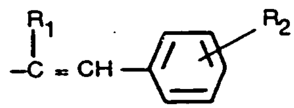
3. A use as claimed in Claim 1 wherein the drug is processed into a form for non-oral administration.

4. An antiulcer drug containing as an active ingredient a 2,3-butanediol diester derivative, other than coixenolide, represented by the formula (I):

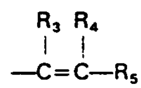


(I)

where R_A is a saturated or unsaturated alkyl group which may have a branched chain, or a group represented by



(where R_1 is a hydrogen atom, cyano group, or lower alkyl group, and R_2 is a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy group, or lower acyloxy group); R_B is a saturated or unsaturated alkyl group which may have a branched chain, phenyl group which may be substituted with lower alkyl group, lower alkoxy group or halogen atom, phenylalkyl group, phenylpropenyl group, phenoxyalkyl group, or a group represented by

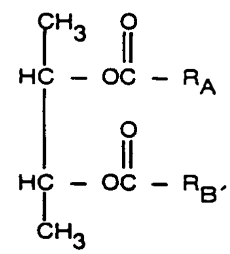


(where R_3 is a hydrogen atom, halogen atom, cyano group, lower alkyl group, or phenyl group, and R_4 is a hydrogen atom, lower alkyl group, or phenyl group, and R_5 is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group, acyloxy group or halogen atom).

5. A drug as claimed in Claim 4 wherein the drug is in the form for oral administration.

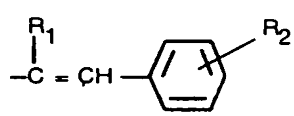
6. A drug as claimed in Claim 4 wherein the drug is in the form for non-oral administration.

7. A 2,3-butanediol diester derivative represented by the formula (II):

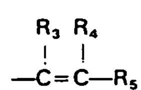


(II)

where R_A is a saturated or unsaturated alkyl group which may have a branched chain, or a group represented by

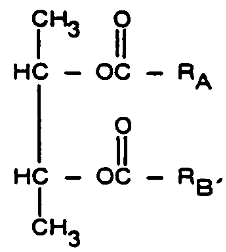


(where R_1 is a hydrogen atom, cyano group, or lower alkyl group, and R_2 is a hydrogen atom, halogen atom, lower alkyl group, lower alkoxy group, or lower acyloxy group); R_B' is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group or halogen atom, phenylalkyl group, phenylpropenyl group, phenoxyalkyl group, or a group represented by



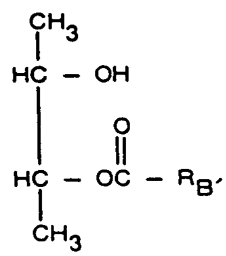
(where R_3 is a hydrogen atom, halogen atom, cyano group, lower alkyl group, or phenyl group, and R_4 is a hydrogen atom, lower alkyl group, or phenyl group, and R_5 is a phenyl group which may be substituted with lower alkyl group, lower alkoxy group, acyloxy group or halogen atom).

8. A process for preparing a 2,3-butanediol diester derivative represented by the formula (II):



(II)

where R_A and R_B' are as defined in claim 7, said process comprising reacting a 2,3-butanediol monoester derivative represented by the formula (VII):



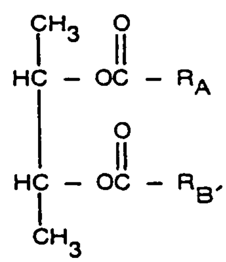
(VII)

where R_B' is as defined above with a carboxylic acid or a reactive derivative thereof represented by the formula (IV):

$$R_ACOOH \qquad (IV)$$

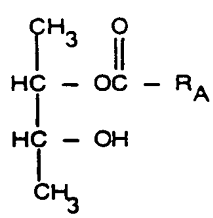
where R_A is as defined above.

9. A process for preparing a 2,3-butanediol diester derivative represented by the formula (II):



(II)

where R_A and R_B' are as defined in claim 7, said process comprising reacting a 2,3-butanediol monoester derivative represented by the formula (V):



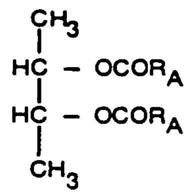
(V)

where R_A is as defined above with a carboxylic acid or a reactive derivative thereof represented by the formula (IV):

$$R_B'COOH \qquad (VI)$$

where R_B' is as defined above.

10. A process for preparing a 2,3-butanediol diester derivative represented by the formula (I'):



(I')

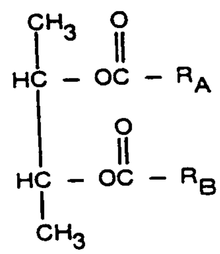
where R_A is as defined in claim 1, said process comprising reacting a 2,3-butanediol with a carboxylic acid or a reactive derivative thereof represented by the formula (IV):

$$R_ACOOH \qquad (IV)$$

where R_A is as defined above.

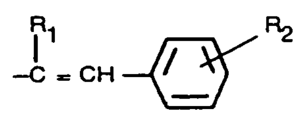
Patentansprüche

1. Verwendung eines 2,3-Butandioldiesterderivates der folgenden allgemeinen Formel (I)

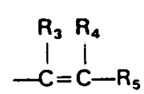


(I)

in der R_A für eine gesättigte oder ungesättigte Alkylgruppe steht, welche eine verzweigte Kette aufweisen kann, oder für eine Gruppe der Formel



(in der R_1 für ein Wasserstoffatom, eine Cyanogruppe oder eine niedere Alkylgruppe steht und in der R_2 für ein Wasserstoffatom, ein Halogenatom, eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine niedere Acyloxygruppe steht); wobei R_B eine gesättigte oder ungesättigte Alkylgruppe bedeutet, welche verzweigt sein kann, oder eine Phenylgruppe, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder ein Halogenatom substituiert sein kann, eine Phenylalkylgruppe, eine Phenylpropylgruppe, eine Phenoxyalkylgruppe oder eine Gruppe der Formel

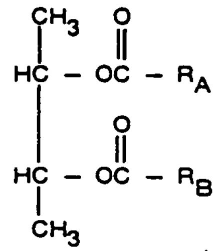


(in der R_3 für ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine niedere Alkylgruppe, eine Phenylgruppe und R_4 für eine Wasserstoffatom, eine niedere Alkylgruppe oder eine Phenylgruppe und R_5 für eine Phenylgruppe steht, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine Acyloxygruppe oder ein Halogenatom substituiert sein kann), zur Herstellung eines Anti-Ulcus-Mittels.

2. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß das Mittel für orale Verabreichung zubereitet wird.

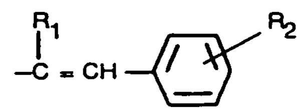
3. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß das Mittel für nicht-orale Verabreichung zubereitet wird.

4. Anti-Ulcus-Mittel, enthaltend als Wirkstoff ein 2,3-Butandioldiesterderivat, ausgenommen Coixenolid, der folgenden Formel (I)

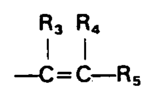


(I)

in der R_A für eine gesättigte oder ungesättigte Alkylgruppe steht, welche eine verzweigte Kette aufweisen kann, oder für eine Gruppe der Formel



(in der R_1 für ein Wasserstoffatom, eine Cyanogruppe oder eine niedere Alkylgruppe steht und in der R_2 für ein Wasserstoffatom, ein Halogenatom, eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine niedere Acyloxygruppe steht); wobei R_B eine gesättigte oder ungesättigte Alkylgruppe bedeutet, welche verzweigt sein kann, oder eine Phenylgruppe, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder ein Halogenatom substituiert sein kann, eine Phenylalkylgruppe, eine Phenylpropylgruppe, eine Phenoxyalkylgruppe oder eine Gruppe der Formel

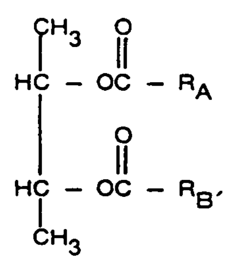


(in der R_3 für ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine niedere Alkylgruppe, eine Phenylgruppe und R_4 für eine Wasserstoffatom, eine niedere Alkylgruppe oder eine Phenylgruppe und R_5 für eine Phenylgruppe steht, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine Acyloxygruppe oder ein Halogenatom substituiert sein kann).

5. Mittel nach Anspruch 4, dadurch gekennzeichnet, daß es für orale Verabreichung vorgesehen ist.

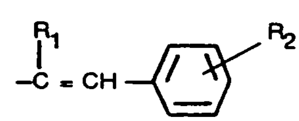
6. Mittel nach Anspruch 4, dadurch gekennzeichnet, daß es für nicht-orale Verabreichung vorgesehen ist.

7. 2,3-Butandioldiesterderivat der allgemeinen Formel (II)

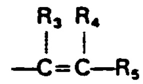


(II)

in der R_A für eine gesättigte oder ungesättigte Alkylgruppe steht, welche eine verzweigte Kette aufweisen kann, oder für eine Gruppe der Formel

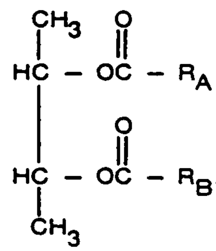


(in der R_1 für ein Wasserstoffatom, eine Cyanogruppe oder eine niedere Alkylgruppe steht und in der R_2 für ein Wasserstoffatom, ein Halogenatom, eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine niedere Acyloxygruppe steht); wobei R_B' eine Phenylgruppe bedeutet, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder ein Halogenatom substituiert sein kann, eine Phenylalkylgruppe, eine Phenylpropenylgruppe, eine Phenoxyalkylgruppe oder eine Gruppe der Formel

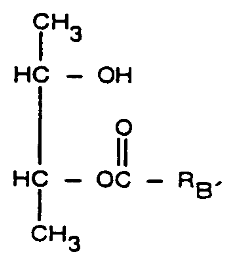


(in der R_3 für ein Wasserstoffatom, ein Halogenatom, eine Cyanogruppe, eine niedere Alkylgruppe, eine Phenylgruppe und R_4 für eine Wasserstoffatom, eine niedere Alkylgruppe oder eine Phenylgruppe und R_5 für eine Phenylgruppe steht, welche durch eine niedere Alkylgruppe, eine niedere Alkoxygruppe oder eine Acyloxygruppe oder ein Halogenatom substituiert sein kann).

8. Verfahren zur Herstellung eines 2,3-Butandioldiesterderivates der Formel (II)



wobei R_A und R_B' die in Anspruch 7 angegebene Bedeutung haben, dadurch gekennzeichnet, daß man ein 2,3-Butandiolmonoesterderivat der Formel (VII)



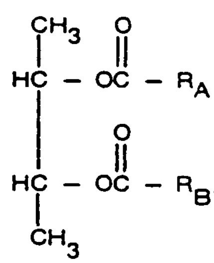
(VII)

wobei R_B' die oben angegebene Bedeutung hat, mit einer Carbonsäure oder einem reaktiven Derivat derselben der Formel (IV)

$$R_ACOOH \qquad (IV)$$

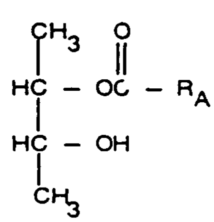
umsetzt, wobei R_A die oben angegebene Bedeutung hat.

9. Verfahren zur Herstellung eines 2,3-Butandioldiesterderivates der Formel (II)



(II)

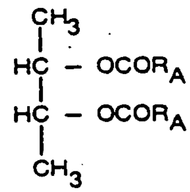
wobei R_A und R_B' die in Anspruch 7 angegebene Bedeutung haben, dadurch gekennzeichnet, daß man ein 2,3-Butandiolmonoesterderivat der Formel (V)



(V)

in der R_A die oben angegebene Bedeutung hat, mit einer Carbonsäure oder einem reaktiven Derivat derselben der Formel (IV)

$$R_B'COOH \qquad (VI)$$



(I')

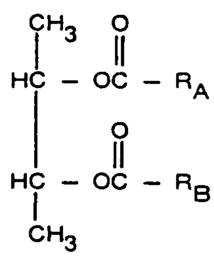
wobei die in Anspruch 1 angegebene Bedeutung hat, dadurch gekennzeichnet, daß man ein 2,3-Butandiol mit einer Carbonsäure oder einem reaktiven Derivat derselben gemäß Formel (IV) umsetzt

$$R_ACOOH \qquad (IV)$$

wobei R_A die oben angegebene Bedeutung hat.

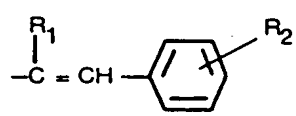
Revendications

1. Utilisation dans la fabrication d'un médicament antiulcéreux, d'un dérivé diester de 2,3-butanediol représenté par la formule (I):

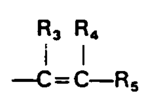


(I)

dans laquelle R_A est un groupe alkyle saturé ou insaturé qui peut avoir une chaîne ramifiée, ou un groupe représenté par



(où R_1 est un atome d'hydrogène, le groupe cyano ou un groupe alkyle inférieur, et R_2 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle inférieur, un groupe alcoxy inférieur ou un groupe acyloxy inférieur); R_B est un groupe alkyle saturé ou insaturé qui peut avoir une chaîne ramifiée, un groupe phényle qui peut être substitué par un groupe alkyle in férieur, un groupe alcoxy inférieur ou un atome d'halogène, un groupe phénylalkyl, un groupe phénylpropényle, un groupe phénoxyalkyle ou un groupe représenté par

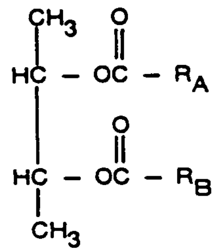


(où R_3 est un atome d'hydrogène, un atome d'halogène, le groupe cyano, un groupe alkyle inférieur ou le groupe phényle, R_4 est un atome d'hydrogène, un groupe alkyle inférieur ou le groupe phényle et R_5 est un groupe phényle qui peut être substitué par un groupe alkyle inférieur, un groupe alcoxy inférieur, un groupe acyloxy ou un atome d'halogène).

2. Utilisation selon la revendication 1, caractérisée en ce que le médicament est traité pour être mis sous une forme convenable pour l'administration par voie orale.

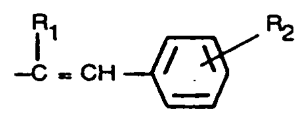
3. Utilisation selon la revendication 1, caractérisée en ce que le médicament est traité pour être mis sous une forme convenable pour une administration par voie non orale.

4. Médicament anti-ulcéreux contenant à titre d'ingrédient actif, un dérivé diester de 2,3-butanediol, autre que le coixénolide, représenté par la formule (I)

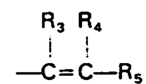


(I)

dans laquelle R_A est un groupe alkyle saturé ou insaturé qui peut avoir une chaîne ramifiée, ou un groupe représenté par



(où R_1 est un atome d'hydrogène, le groupe cyano ou un groupe alkyle inférieur, et R_2 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle inférieur, un groupe alcoxy inférieur ou un groupe acyloxy inférieur); R_B est un groupe alkyle saturé ou insaturé qui peut avoir une chaîne ramifiée, un groupe phényle qui peut être substitué par un groupe alkyle in férieur, un groupe alcoxy inférieur ou un atome d'halogène, un groupe phénylalkyle, un groupe phénylpropényle, un groupe phénoxyalkyle ou un groupe représenté par

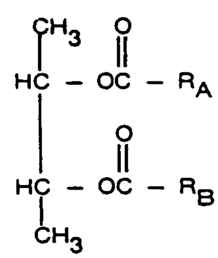


(où R_3 est un atome d'hydrogène, un atome d'halogène, le groupe cyano, un groupe alkyle inférieur ou le groupe phényle, R_4 est un atome d'hydrogène, un groupe alkyle inférieur ou le groupe phényle et R_5 est un groupe qui peut être substitué par un groupe alkyle inférieur, un groupe alcoxy inférieur, un groupe acyloxy ou un atome d'halogène).

5. Médicament selon la revendication 4, caractérisé en ce que le médicament se présente sous une forme convenable pour l'administration par voie orale.

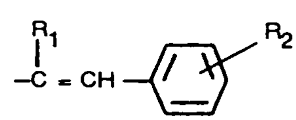
6. Médicament selon la revendication 4, caractérisé en ce que le médicament se présente sous une forme convenable pour l'administration par voie non orale.

7. Dérivé diester de 2,3-butanediol représenté par la formule (II):

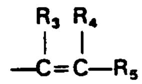


(II)

dans laquelle R_A est un groupe alkyle saturé ou insaturé qui peut avoir une chaîne ramifiée, ou un groupe représenté par

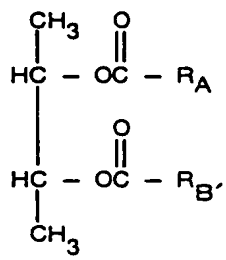


(où R_1 est un atome d'hydrogène, le groupe cyano ou un groupe alkyle inférieur, et R_2 est un atome d'hydrogène, un atome d'halogène, un groupe alkyle inférieur, un groupe alcoxy inférieur ou un groupe acyloxy inférieur); R_B' est un groupe phényle qui peut être substitué par un groupe alkyle inférieur, un groupe alcoxy inférieur ou un atome d'halogène, un groupe phénylalkyle, un groupe phénylpropényle, un groupe phénoxyalkyle ou un groupe représenté par



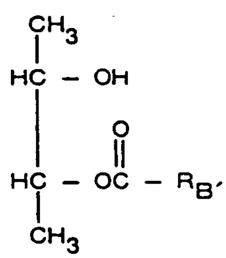
(où R_3 est un atome d'hydrogène, un atome d'halogène, le groupe cyano, un groupe alkyle inférieur ou le groupe phényle, R_4 est un atome d'hydrogène, un groupe alkyle inférieur ou le groupe phényle, et R_5 est un groupe phényle qui peut être substitué par un groupe alkyle inférieur, un groupe alcoxy inférieur, un groupe acyloxy ou un atome d'halogène).

8. Procédé de préparation d'un dérivé diester de 2,3-butanediol représenté par la formule (II)



(II)

dans laquelle R_A et R_B' sont tels que définis dans la revendication 7, caractérisé en ce qu'il comporte la réaction d'un dérivé monoester de 2,3-butanediol représenté par la formule (VII):



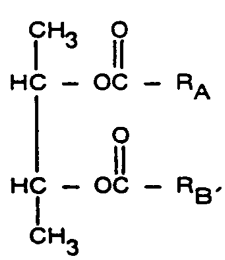
(VII)

dans laquelle R_B' est tel que défini ci-dessus, avec, un acide carboxylique ou un de ses dérivés réactifs représenté par la formule (IV):

$$R_ACOOH \qquad (IV)$$

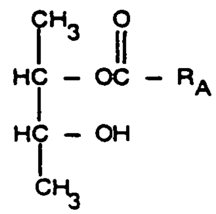
dans laquelle R_A est tel que défini ci-dessus.

9. Procédé de préparation d'un dérivé diester de 2,3-butanediol représenté par la formule (II)



(II)

dans laquelle R_A et R_B' sont tels que définis dans la revendication 7, caractérisé en ce qu'il comporte la réaction d'un dérivé monoester de 2,3-butanediol représenté par la formule (V):



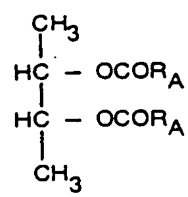
(V)

dans laquelle R_A est tel que défini ci-dessus, avec un acide carboxylique ou un de ses dérivés réactifs représenté par la formule (VI):

$$R_B'COOH \qquad (VI)$$

dans laquelle R_B' est tel que défini ci-dessus.

10. Procédé de préparation d'un dérivé diester de 2,3-butanediol représenté par la formule (I')



(I')

dans laquelle R_A est tel que défini dans la revendication 1, caractérisé en ce qu'il comporte la réaction du 2,3-butanediol avec un acide carboxylique ou un de ses dérivés réactifs représenté par la formule (IV):

$$R_ACOOH \qquad (IV)$$

dans laquelle R_A est tel que défini ci-dessus.